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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,728	05/24/2001	Sandra J. Rosenthal	11672N/020878	2786

32885 7590 12/29/2003

STITES & HARBISON PLLC
424 CHURCH STREET
SUITE 1800
NASHVILLE, TN 37219-2376

EXAMINER

CEPERLEY, MARY

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 12/29/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/864,728

Applicant(s)

ROSENTHALL ET AL.

Examiner

Mary (Molly) E. Ceperley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-16 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 8-16 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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1) The amendment to page 34, after line 14 has not been entered since the proposed location of its entry is incorrect. It would appear that the amendment should be to page 24 rather than page 34.

2) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3) Although specific claims are cited in the rejections below, these rejections are also applicable to all other claims in which the noted problems/language occur.

4) Claims 8-16 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in paragraph **7)** of the May 01, 2003 Office action.

Applicants' arguments filed October 03, 2003 have been fully considered but they are not persuasive. Applicants' arguments made at pages 16 and 17 of the Remarks are not germane to the rejection at issue. The examiner has not made any statement that she "doubts the truth or accuracy of any statement" made in the specification nor is there any reason why the examiner must "produce any evidence of the TOPO's required presence". The rejection is made on a scope of enablement ground, i.e. that there is enablement present only for the preparation of nanocrystal conjugates as described in paragraph **7)** of the rejection. The examiner has reread the specification in its entirety and finds no other description of how to prepare any of the claimed conjugates. Applicants' remarks in paragraph **9.(b)** of the October 03, 2003 response state that "sulfur is attached by electrostatic interactions in a manner similar to which thiols are attached to gold surfaces or nanoparticles". However, the specification provides no such description of any "electrostatic interactions". U.S. Patent Nos. 6,221,602 and 6,306,610 which are relied upon by applicants to support how to make the claimed conjugates (October 03, 2003 Remarks, **(d)**, page 19) have effective dates after the provisional application 60/206,771 to which the instant application claims priority and therefore these patents do not provide support for any method of preparation. With regard to U.S. Patent No. 5,990,479, the instant specification at page 42,

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lines 21 and 22, recites only that "the nanocrystal compounds of the present invention may be used in the assays described in US Patent 5,990,479". No statement is made in the specification that any method of preparation used in U.S. Patent 5,990,479 is applicable to the production of the claimed conjugates (see also, page 5, line 21 – page 6, line 2 of the instant specification). However, it is noted that the method of U.S. Patent 5,990,479 requires the use of a tris-octyl-phosphine oxide coating (col. 7, lines 54-63 and the working examples).

5) Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The newly added term "nanocrystal compound comprising the following formula" renders claim 8 indefinite since it cannot be determined what other components/moieties are present on the compound of formula (I) other than those which are specified by the depicted structure.

6) Claims 8-16 are again rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) This rejection is maintained for the reason stated in paragraph **9)b)** of the May 01, 2003 Office action. It is presumed that applicants' remarks made in regard to "R3" are in fact made in regard to "R" (Remarks, page 19). As stated by applicants, "R3 [sic] is part of the linker arm portion of the compound that is attached to the nanocrystal, Y". However, as clearly depicted in formula (I), "R" contains two covalent bonds, one for attachment to the "Y" moiety and the other for attachment to the remainder of the linker moiety. Hence, "R" defined as "a bond" is appropriate but "R" defined as any terminal "-SH" moiety is inconsistent with the structural requirements of formula (I).

b) This rejection is maintained for the reason stated in paragraph **9)d)** of the May 01, 2003 Office action. Consistent with the statement in the paragraph **a)** directly above, since "R"

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is a linking moiety, it appears that the -SH group must be reacted with some (unspecified) functional group on the nanocrystal. The same problem exists for "R2" defined as the non-terminal moiety -SH. Applicants' statements made in paragraph **(d)** of page 19 of the October 03, 2003 Remarks are addressed in paragraph **4)** above.

7) Claims 8-10 and 12-15 are again rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 25-33 and 37 of copending application no. 09/864,731 for the reasons of record. Applicants have not specifically traversed this rejection but have requested that the rejection be held in abeyance until there is an indication of allowable subject matter in at least one of the applications in question.

8) Claims 8-16 are again rejected under 35 U.S.C. 103(a) as being unpatentable over each of Bruchez et al (U.S. 6,274,323) or Bawendi et al (U.S. 6,306,610) for the reasons state in paragraph **14)** of the May 01, 2003 Office action.

Applicants' arguments filed October 03, 2003 have been fully considered but they are not persuasive. Applicants do not contest the examiner's statement that it would be obvious to substitute the known drugs melatonin and serotonin for other equivalent drugs in the drug-nanocrystal conjugates of Bruchez et al and Bawendi. Therefore it is assumed that applicants allege no criticality for the drug portion of the nanocrystal-drug conjugates. Applicants argue that "one skilled in the art would ... not be motivated to modify this disclosure to arrive at the present invention". However, this argument does not address the rejection at issue wherein no modification of the described conjugates is required. The references describe nanocrystal-drug conjugates which contain the same linkers as those used in the instantly claimed conjugates, for example, PEG linkers (polyether linker arms) which are clearly encompassed by the linkers of formula (I) of instant claim 8 wherein the linker may be defined as $-\text{CH}_2-\text{CH}_2-(\text{OCH}_2\text{CH}_2)_p-\text{O}(\text{CH}_2\text{CH}_2)-$, i.e. a PEG linker. See the description of the references in paragraph **14)** of the May 01, 2003 Office action.

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9) Claims 8-16 are again rejected under 35 U.S.C. 103(a) as being unpatentable over **a)** each of Bruchez et al (U.S. 6,274,323) or Bawendi et al (U.S. 6,306,610) taken in combination with each of **b)** Zalipsky (Bioconjugate Chem. (1995)) or Zalipsky et al (Eur. Polym. J. (1983) for the reasons of record (see paragraph **15)** of the May 01, 2003 Office action).

The remarks regarding references **a)** in paragraph **8)** above are applicable to this rejection as well. Applicants' argument that there is no reason provided for modifying the primary references misses the point of the rejection at issue for the reason stated in paragraph **8)** above. The Zalipsky references are applied for their teaching that a variety of terminal functional groups, including those used in the instant invention, may be present on the PEG linker to attach PEG to biologically active molecules. Applicants have not argued that any particular type of terminal functional group on the PEG moiety is in any way critical to the practice of the invention.

10) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

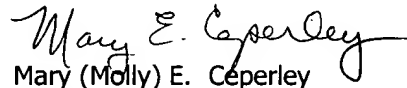
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11) Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary (Molly) E. Ceperley whose telephone number is (703) 308-4239. The examiner can normally be reached from 8 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556 or (703) 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

December 27, 2003


Mary (Molly) E. Ceperley
Primary Examiner
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